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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/917,800	MENDRICK ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *October 02, 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-91* is/are pending in the application.

4a) Of the above claim(s) *90 and 91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *55-91* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/11/01; 2/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments filed October 02, 2003 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. The withdrawal of claims 90 and 91 has been acknowledged.

3. Claims 55-89, alpha-naphthylisothiocyanate (ANIT) as the toxin and liver as the tissue, are examined on the merits.

4. FINAL OFFICE ACTION.

IDS

5. A duplicate copy of the PTO Form 1449, filed October 11, 2001, comprising the listing of the Foreign Patent Documents that were previously lined through in the Office Action, mailed May 02, 2003, has been received, October 20, 2004, via facsimile by the Examiner. The documents listed on said duplicate copy have been considered.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 55-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. This rejection is necessitated by Applicants amendments.

9. Claims 55, 86, and 88, step (b), recite the newly added limitation of "quantitative gene expression...of the test compound" which has not been found in the instant specification. It is noted that the pointed to support of page 40, line 29, through page 42, line 14, provides disclosure for linear discriminant analysis as directed to tox and nontox samples which is different from the newly added limitation of "information from a control liver cell or tissue sample exposed to the toxin excipient." Claims 55-85, 87, and 89 rejected for being dependent from claim 55, 86, or 88.

10. Claim 62, line 3, recites "the mean expression level for that gene in the toxin-exposed cell or tissue samples" has not been found in the instant specification. It is noted that the pointed to support provides disclosure as being directed to the "average across the corresponding samples" (page 40, line 20) which is different from the limitation of "the mean expression level for that gene in the toxin-exposed cell". Further, the disclosure of "the expression levels from a gene or genes from Tables 1-3 may be compared to the expression levels found in tissues or cells exposed to the toxins described" is different from the limitation of "the mean expression level for that gene in the toxin-exposed cell".

11. Claim 77, line 3-4, recites the limitation of "control liver cell or tissue samples that have been exposed to the excipient" has not been found in the instant specification. It is noted that the term "excipient" has been reasonably construed as an inert substance used as a diluent or vehicle for a drug. Further, the pointed to support in the instant specification provides

disclosure for "control compositions were administered...using administration diluents" (page 36, lines 5-7) wherein the compositions have been reasonable construed to comprise at least the administration diluents and a composition. Therefore, the broad limitation of "excipient" is different from the pointed to support for said limitation.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 55-89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. This rejection is maintained with respect to claims 55-89, as recited in the previous office action mailed May 02, 2003.

15. Specific to claims 55, 86, and 88, step (b), the phrase "comparing the gene expression profile to a database" causes the claims to be vague and indefinite. The step of comparing is unclear because it is uncertain what is being compared in step (b). Is the comparison in step (b) comparing expression profile to the whole database or to a specific data set contained within the database? Clarification of the metes and bounds of the claims are required. Claims 56-85, 87, and 89 are rejected from being directly or indirectly dependent from claims 55, 86, or 88.

RESPONSE TO ARGUMENT

16. Applicant argues that the claim amendment to step (b) of claims 55, 86, and 88 has resolved that vague and indefinite issue discussed above. Applicant's argument has been

fully considered and found to be unpersuasive because step of comparing remains unclear as uncertain what is being compared in step (b) as discussed above.

17. Specific to claim 81, line 2, the term "quantifies" causes the claim to be vague and indefinite. It is unclear how information can actively "quantifies" the ability of a gene to accomplish a specific task. Clarification of the metes and bounds of the claims are required.

RESPONSE TO ARGUMENT

18. Applicant argues that the claim amendment has resolved that vague and indefinite issue discussed above. Applicant's argument has been fully considered and found to be unpersuasive because claim 81 remains unclear as to how information can actively "quantifies" the ability of a gene to accomplish a specific task.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 55-58, 62-70, 72-79, 81, and 84-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al. (US 6218122 B1) taken with Cunningham et al. (US 6372431 B1).

22. This rejection is maintained with respect to claims 55-58, 62-70, 72-76, 78, 79, 81, and 84-88, as recited in the previous office action mailed May 02, 2003.

23. It is noted that claims 59 and 60 have been withdrawn from the instant rejection due to the inclusion of the claims in the previous Office Action, mailed May 02, 2003, had been an inadvertent typographical error.

24. The instant rejection has been extended to claim 77 as necessitated by Applicant's claim amendment to said claim.

RESPONSE TO ARGUMENT

25. Applicant argues that Friend et al. does not disclose or suggest a database of animal liver gene expression levels containing toxin-exposed and control excipient-exposed samples that are used to predict a toxic effect of a test compound or hepatoxicity resulting from exposure to a test compound. Applicant argues that Friend et al. does not disclose the comparing gene expression levels, a profile of gene expression levels..., or a profile of control samples, to predict toxic effect...to a test compound. Further, Applicant argues that Cunningham et al. alone or combined with Friend et al. does not address the deficiencies of Friend et al. Applicant's arguments have been fully considered and found to be unpersuasive.

26. Friend et al. describes an improvement that would result in significant benefit to the treatment of disease by monitoring early changes in cell activities (column 2, lines 12-31) or organ functions such as kidney, liver or hear (column 1, lines 55-62). The improvement of

Friend et al. is directed to monitoring beneficial effects or adverse effects of therapies such as toxic effects of a therapy from one or more drugs by providing databases comprising response profile data for one or more therapies (column 3, lines 41-65).

27. Cunningham et al. describes a method for screening compounds and therapeutics for metabolic responses indicative of a toxic compound or molecule (Abstract) such as hepatoxin (column 7, line 43-50). The method of Cunningham et al. comprises administering rats with test compounds or DMSO (excipient) as control. Messenger RNA isolated from tissues of rats treated with the test compounds or DMSO alone (excipient). Quantitative and differential expression profiles are determined from said mRNA (columns 22-23, §VII Target Preparation). One of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement described by Friend et al. and provide a database comprising the expression profiles of Cunningham et al. to determine the toxic effect of test compounds. Therefore, the teaching of Friend et al. and Cunningham et al. would have render the claimed invention obvious over the prior art.

REJECTION RE-ITERATED

28. Friend et al. describes a method for predicting response profiles (expression profile) to toxins by measuring a plurality of cellular constituents that indicate aspects of the biological state of a cell (column 9, lines 15-38), as in claim 81.

29. Expression profile data are loaded into the computer system, which cause the execution of expression profile analysis software to determine the difference between diagnostic profile, and a response profile determined from the perturbation response profile data

contained in a database (columns 13, lines 45-55 and 19, lines 17-38), as in instant claims 55, step (b), 57, 75, 78, 79, and 86-88.

30. The method of Friend et al. comprises expression profiles established for approximately 6000 genes (column 10, lines 40-42). The differential expression of the 6000 genes exposed to a drug (column 11, lines 40-45), as in instant claims 64-67, 73, and 74.

31. Microarrays were prepared with probes generated by PCR reactions (column 22, lines 37-51). Two different cells are hybridized to the microarray; one cell type exposed to a drug or toxin another not exposed to a drug or toxin (control) (column 21, lines 52-56), as in instant claims 68-70.

32. However, Friend et al. does not describe the toxin, ANIT, or an external database.

33. Cunningham et al. describes a method for screening compounds and therapeutics for metabolic responses indicative of a toxic compound or molecule (Abstract) such as hepatoxin (column 7, line 43-50), as in instant claim 85.

34. The toxic compounds may include ANIT affecting the liver (column 2, lines 1-8), as in instant claims 55, step a), and claims 56 and 72.

35. Tables 1-10 disclose differential expression of genes correlated to liver pathology, as in instant claim 58.

36. The method of Cunningham et al. comprises administering rats with test compounds or DMSO (excipient) as control. Messenger RNA isolated from tissues of rats treated with the test compounds or DMSO alone (excipient). Quantitative and differential expression profiles are determined from said mRNA (columns 22-23, §VII Target Preparation). The fluorescence signal within each element was then integrated to obtain a numerical value

corresponding to the average intensity of the signal (column 24, lines 15-19), as in instant claims 62, 63, and 77.

37. The ESTs are derived from the ZOOSEQ database (column 9, lines 14-16), as in instant claim 76.

38. Acetaminophen is a widely-used analgesic which is metabolized by specific cytochrome P450 isozymes with the majority of the drug undergoing detoxification by glucuronic acid, sulfate and glutathione conjugation pathways (column 1, lines 37-40), as in instant claim 84.

39. One of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement described by Friend et al. for a method of using expression profiles for early diagnosis or prognosis which may be resulted from exposure to a toxin (column 6, lines 49-54), and provide a database comprising the expression profiles of Cunningham et al. to determine the toxic effect of test compounds such as ANIT. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the method of Friend et al. for predicting response profiles (expression profile) to ANIT as taught by Cunningham et al.

CONCLUSION

40. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

41. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until

after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

42. This application contains claims 90 and 91 drawn to an invention nonelected with traverse filed March 05, 2003. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

43. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

44. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and

history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

45. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

46. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

47. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

C. Dune Ly

11/23/04

MICHAEL P. WOODWARD
SUPERVISORY PATENT EXAMINER
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11/29/04